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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/897,584	06/29/2001	Robert S. DeWitte	426.97.265	3885

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EXAMINER
LY, CHEYNE D

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 05/12/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/897,584	DEWITTE ET AL.	
	Examiner	Art Unit	
	Cheyne D Ly	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-4 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-4 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election with traversal of Group I, claims 1-4, in Paper No.8, filed March 04, 2003, is acknowledged.

2. It is acknowledged that claims 5-20 have been cancelled; therefore, Applicant's traversal of the restriction requirement is moot.

3. The requirement is still deemed proper and is therefore made FINAL.

4. Claims 1-4 are examined on the merits.

Priority

5. In order for the present application to receive benefit of priority for an invention to an earlier application, the earlier application (parent or provisional) must disclose the invention so as to be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112 regarding said invention. See Transco Products, Inc. v. Performance Contracting, Inc., 38 F.3d 551, 32 USPQ 2d 1077 (Fed. Cir. 1994). The specific claimed subject matter of the present application was not disclosed in the priority document (Application Number 08/741,866). Therefore, domestic priority under 35 U.S.C. §§ 120 and/or 121 has not been granted for the presently claimed subject matter.

Specification

6. The title of the invention is not descriptive. The title is objected to because the title is directed to a system and method for structure-based design that includes accurate prediction of binding free energy, however, the claims are directed to a method of de novo designing molecules that bind to a receptor site on a protein. A new title is required that is clearly indicative of the invention to which the claims are directed.

Claim Rejections - 35 USC § 101

7. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

8. Claims 1-4 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory algorithm type subject matter.

9. It is acknowledged that the claim subject matter is a method of de novo designing molecules based on free energy. However, claims 1-4 are rejected because they are directed to a non-statutory subject matter due to lacking any physical steps such as displaying the molecule, which has been designed. Currently, the steps are merely algorithmic processes of manipulating data directed to a molecule with its receptor without providing a means of visualizing the results of the said processes; therefore, the claim subject matter lacks a real world value. The critical steps of displaying the designed molecule would cause the subject matter in its entirety to be a practical application.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

12. Specific to claim 1, steps (b) and (e), different types of ranking are cited in steps (b) and (e), however, it is unclear as to what is meant in step (e) as to whether the ranking of step(b) is utuilized or not. Clarification of the metes and bounds is required.

13. Claim 1 is regarded as indefinite because the method of the preamble differs from the active steps in the claim. The active steps of the claim support a method of building a molecule. However, the active steps of each claim do not accomplish the intended goal of the method, which is to design molecules de novo. Which component, the preamble or the active steps, of the claim control the metes and bounds of the claim? Currently, it is inconclusive as to which component is controlling the claims or how one is to design molecules de novo.

14. Claims 2-4 are rejected for the same reasons as for claim 1 due to being dependent from claim 1.

LACK OF ENABLEMENT UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

15. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

16. Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for de novo design of molecules that interact with receptor sites of Src-homology-3 domain, Src-homology-2 domain, MDM2 protein, CD4 protein, or human carbonic anhydrase II protein, does not reasonably provide enablement for de novo design of molecules that interact with any receptor. Further, the instant specification is not enabling for the de novo design of any molecule to interact with any receptor site. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

17. Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a prima facie case is discussed below.

18. Applicant discloses information present in crystal structures of proteins and crystal structures of protein-ligand may be used for predicting binding free energy which is necessary for the method of the claimed invention (Page 22, lines 19-22 to page 23, lines 1-4). It is acknowledged that the applicants have disclosed information to enable one skilled in the art to calculate the binding free energy for the molecules that interact with receptor sites of Src-homology-3 domain, Src-homology-2 domain, MDM2 protein, CD4 protein, or human carbonic anhydrase II protein (Example 2, pages 56-79).

19. However, it is well documented that protein crystallization is in essence a trial-and-error method, and the results are usually unpredictable (Drenth, J.). Further, as recently as November 1, 2002, Science published a New Focus article depicting the current state of the art for protein

crystallization that supports the unpredictability of the art. In essences, protein crystallization is still a trial and error process because the current technology for producing protein for the crystallization process is unpredictable, which results in high failure rate for proteins that are being crystallized. Therefore, researchers continue to have trouble generating sufficient protein required for the crystallization process (New Focus, Science, 2002). In light of the difficulty of the protein crystallization process, it is, therefore, unreasonable to expect one skilled in the art to use the method that relies on data that was derived from an unpredictable process such as protein crystallization for de novo molecule design of that interacts with any receptor site without undue experimentation.

Claim Rejections - 35 USC § 102

20. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

21. Claims 1, 3, and 4 are rejected under 35 U.S.C. 102(b) as being clearly by anticipated by DeLisi et al. (US 5,495,423 A).

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

22. Delisi et al. discloses a method of drug design. The factors that contribute to the said design process are surface complementary, ...electrostatic interaction energy, and solvation free energy (column 1, lines 39-44). In designing a peptide to bind to a receptor site, a peptide is docked to the receptor, each amino acid is placed in various orientations at each grid point, calculate the electrostatic interaction energy, those low-energy positions are selected, rank the

positions according to the minimized energies, the backbone between the terminal anchor residues is filled in, and the peptide is manufactured (Column 5, lines 22-65 to column 6, lines 3-27), as in claim 1, steps (a)-(c). The minimum energy locations for the charged end-residue is determined using a multi-copy mean-field energy minimization algorithm. A multi-copy mean-field approximation algorithm has been written as a modification of the software CHARMm Molecular modeling is performed with software ECEPP (Empirical Conformational Energy Program for Peptides, from Indiana University) (Column 10, lines 66-67 to column 11, lines 1-15), as in claims 1, step (d)-(g), 3 and 4.

Claim Rejections - 35 USC § 103

23. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

24. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

25. Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over DeLisi et al. (US 5,495,423 A) in view of In re Gulack, 703 F.2d 1381, 1385, 217 USPQ 401, 404 (Fed. Cir. 1983).

26. DeLisi et al. discloses the limitations directed toward claim 1 as cited above. Even though the method disclosed by Delisi et al. does not specify that the receptor site is a Src-homolgy-2 domain, the specific limitations of Src-homolgy-2 (SH2) domain in this instant case do not distinguish the invention from the prior art in term of patentability because they are descriptive nonfunctional subject matter.

27. In re Gulack defines nonfunctional descriptive material, as when descriptive material is not functionally related to the substrate, the descriptive material will not distinguish the invention from the prior art in term of patentability. Also, the MPEP indicates that descriptive material that cannot exhibit any functional interrelationship with the way in which computing processes are performed does not constitute a statutory process, machine, manufacture or composition (MPEP § 2106 (IV)(B)(b)). Specific to the instant case, the method of de novo designing molecules merely process the data directed toward the Src-homolgy-2 domain without creating any functional interrelationship, either as part of the stored data or as part active steps of the said method, then such descriptive material alone does not impart functionality either to the data as so structured, or to the computer.

28. Clearly, a skilled artisan would have been motivated to partake the concept emphasized by DeLisi et al. for designing de novo molecules based on free energy. Further, the specific limitation of a SH2 domain is regarded as nonfunctional descriptive material as defined by In re Gulack. Therefore, it would have been obvious to one having ordinary skill in the art at the time

of the invention was made to use the crystal structure data for the SH2 domain in the method of DeLisi et al. for designing de novo molecules based on free energy.

29. Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over DeLisi et al. (US 5,495,423 A) in view Hatada et al. (US 6251620 B1).

30. DeLisi et al. discloses the limitations directed toward claim 1 as cited above.

31. However, Delisi et al. does not specify that the receptor site is a Src-homolgy-2 domain.

32. Hatada et al. discloses that the three-dimensional structures of SH2 domain protein have been determined by X-ray crystallography (Abstract).

33. Clearly, a skilled artisan would have been motivated to partake the concept emphasized by DeLisi et al. for designing de novo molecules based on free energy (column 1, lines 39-44) and ligand and receptor interactions (column 1, lines 16-19); and improve on the said method by using the X-ray crystal coordinates of SH2 disclosed by Hatada et al. Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention was made to use the crystal structure data for the SH2 domain in the method of DeLisi et al. for designing de novo molecules based on free energy.

CONCLUSION

34. NO CLAIM IS ALLOWED.

35. Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 193), and 1157

OG 94 (December 28, 1993) (see 37 CFR § 1.6(d)). The CM1 Fax Center number is either (703) 308-4242 or (703) 305-3014.

36. Any inquiry concerning this communication or earlier communications from the examiner should be directed to C. Dune Ly, whose telephone number is (703) 308-3880. The examiner can normally be reached on Monday-Friday from 8 A.M. to 4 P.M.

37. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, Ph.D., can be reached on (703) 308-4028.

38. Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instruments Examiner, Tina Plunkett, whose telephone number is (703) 305-3524 or to the Technical Center receptionist whose telephone number is (703) 308-0196.

C. Dune Ly
5/8/03

ARDIN H. MARSCHEL
PRIMARY EXAMINER